ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 13, Issue 3, 2020

Online - 2455-3891
Print - 0974-2441

Research Article

MEASUREMENT OF ADJUSTED ISCHEMIA-MODIFIED ALBUMIN MARKER IN EARLY PREGNANCY LOSS

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Received: 09 December 2019, Revised and Accepted: 31 December 2019

ABSTRACT

Objective: The objective of the study was to identify the possible association between adjusted ischemia-modified albumin (IMA) marker and early pregnancy loss.

Study Design: This was a case–control study.

Setting: This study was conducted at the Department of Obstetrics and Gynecology of Al-Yarmouk Teaching Hospital.

Methods: The study included 90 pregnant women, aged from 18 to 35 years old, attending the outpatient and inpatient clinic with single fetal pregnancy with a gestational age range between 6th and 12th weeks, they were divided into two groups; Group A included 45 cases with single viable fetus – control group. Group B included 45 cases diagnosed as missed miscarriages at time of enrollment – study group. Serum IMA was measured for patients in both groups.

Results: Adjusted IMA levels increased in normal pregnancy, but it was higher in woman with early pregnancy loss. Cutoff 41.2 ng/mL was used to discriminate between normal pregnancy and early pregnancy loss, with a sensitivity 0.77, specificity 0.51, and accuracy 0.64.

Conclusion: IMA and adjusted IMA levels were elevated in women with early pregnancy loss.

Keywords: Pregnancy loss, Pregnant women, Adjusted ischemia-modified albumin marker.

 DOI: http://dx.doi.org/10.22159/ajpcr.2020.v13i3.36582

INTRODUCTION

Early pregnancy loss denotes a nonviable intrauterine pregnancy in which the gestational sac is empty or contains a fetus with no cardiac activity occurring at or <12 weeks' gestation [1-3]. Miscarriage is common, its incidence about 15% of clinically recognized pregnancies. The actual causes of pregnancy loss frequently unclear [4]. In about 80% of missed miscarriage onset of the maternal placental circulation is both precocious and generalized throughout the placenta. This occurs independent of the karyotype of the conceptus leading to higher O_2 concentrations during early pregnancy, widespread trophoblastic oxidative damage, and placental degeneration [5,6]. Studies suggest that a burst of oxidative stress occurs in the normal placenta as the maternal circulation is established, and speculate that this may serve a physiological role in stimulating normal placental differentiation but may also be a factor in the pathogenesis of pre-eclampsia and early pregnancy failure if antioxidant defenses are depleted [7]. Ischemia-modified albumin (IMA) is serum albumin in which the N-terminus has been chemically modified [8]. Its formed during hypoxia by superoxide free radicals which cause cleavage of the first two amino acids (aspartate-alanine) of N-terminus of the human serum albumin [9]. This modification reduces the affinity of plasma albumin to bind to heavy metal ions such as cobalt, nickel, and copper [10]. IMA is a recently developed biomarker of transient myocardial ischemia. Circulating IMA is increased in patients with myocardial ischemia, after percutaneous coronary intervention, and in acute coronary syndromes [8].

Aim of the study

The aim of the study was to identify the possible association between adjusted IMA marker and early pregnancy loss.

METHODS

Study design

A case–control study was conducted at the Department of Obstetrics and Gynecology of Al-Yarmouk Teaching Hospital in cooperation with the laboratory department of the hospital through a period from February 2018 to October 2018. The study protocol approved by the scientific council of obstetrics and gynecology/Iraqi board for medical specializations.

Women were informed about the nature of the study and verbal consents were taken from all of them.

The study included 90 pregnant women, aged 18–35 years old within the first trimester of pregnancy. Patient were collected from the outpatient clinic and inpatient obstetric ward of Al-Yarmouk Hospital with single fetal pregnancy with a gestational age range between 6th and 12th weeks depending on accurate last menstrual period and early ultrasonography. They were divided into two groups as:

- Group A includes 45 women with uncomplicated pregnancies in their first trimester, which considered as the control group
- Group B includes 45 women diagnosed as missed miscarriages by ultrasound examination at time of enrollment.

Inclusion criteria for the study group

- Single nonviable fetus by ultrasound examination at time of enrollment
- Gestational age within the first trimester between 6th and 12th weeks
- Any parity status.

Exclusion criteria

Current multiple pregnancy, history of medical disease, for example, ischemic disease, diabetes mellitus, heart disease, hypertension, liver

Table 1: Comparison of demographic features of the study groups

Variables	Group B (early pregnancy loss) (n=45)	Group A (normal pregnancy) (n=45)	Total (n=90)	p-value
Age (years) mean±SD	28±7.6	28.2±7.3	28.1±7.4	0.911[t]
Body mass index (kg/m^2) mean±SD	26.9±4.5	27.5±4.4	27.2±4.4	0.525[t]
Gravida, median (range)	3 (1–17)	4 (1–7)	3 (1–17)	0.411[M]
Parity, median (range)	2 (0–16)	2 (0–6)	2 (0–16)	0.598[M]
Number of miscarriages, median (range)	1 (0–1)	1 (0–1)	1 (0–1)	0.526[M]
Gestational age (weeks), mean±SD	9.2±1.7	9±1.8	9.1±1.7	0.589[t]

[M]Mann–Whitney U test, [t]independent t-test. SD: Standard deviation

Table 2: Comparison of serum albumin and ischemia-modified albumin markers between the study groups

Variables	Group B (early pregnancy loss) (n=45)	Group A (normal pregnancy) (n=45)	Total (n=90)	p-value
Serum albumin (g/dl), mean±SD	4.4±0.4	4.5±0.4	4.5±0.4	0.484[t]
Ischemia-modified albumin (ng/ml), median (range)	63.7 (20.1–285.2)	43.4 (1.1–320.3)	52.4 (1.1320.3)	0.004**[M]
Adjusted ischemia-modified albumin (ng/ml), median (range)	63.3 (21.3–331.6)	39.9 (1–385.8)	53.1 (1–385.8)	0.003**[M]

[M]Mann–Whitney U test; [t]independent t-test; **<0.01 significant

Table 3: Correlation between adjusted ischemia-modified albumin concentration and other parameters

Variables	Adjusted ischemia-modified albumin (ng/ml)	
	Correlation coefficient (R)	p-value
Age (years)	−0.141	0.184
Gravida	−0.021	0.846
Parity	−0.021	0.847
Number of miscarriages	−0.05	0.642
Gestational age (weeks)	−0.073	0.494
Body mass index (kg/m^2)	−0.091	0.395
Serum albumin (g/dl)	0.055	0.609

disease, renal disease or any other medical conditions, current smokers, and ectopic pregnancy were excluded from the study.

Clinical assessment

A detailed history was obtained from all patients including name, age, history of present illness, date of last menstrual period, obstetrical history, gynecological history, and medical, surgical and social history.

- General examination including vital sign, weight, height, and body mass index (BMI)
- Abdominal examination and vaginal examination in case of active vaginal bleeding.

Investigations

All participant women were subjected to the following investigations:

- Full blood count
- Coagulation profile
- Liver and renal function test
- Serum albumin
- Blood group and rhesus
- Transabdominal ultrasonography to confirm GA and fetal viability for Group A and missed miscarriage for Group B.

Samples preparation for IMA analysis

Fasting blood sample (5 ml) of venous blood was drawn from each patient by venipuncture and collected in a serum separator tube and was allowed to clot for 2 h at room temperature before centrifugation for 20 min at approximately 1000 rpm. Samples were stored at −20°C or −80°C and analyzed within 3 months of collection.

Samples analysis

Serum IMA concentrations were measured using a quantitative sandwich enzyme immunoassay technique (Human IMA ELISA Kit). Based on biotin double sandwich technology to assay IMA, results were expressed in ng/mL. Serum albumin concentrations measured in our hospital in biochemistry laboratory. Albumin concentrations were expressed as g/dL. Calculation of adjusted IMA concentrations done by following formula:

Adjusted IMA=Individual serum albumin concentrations/median albumin concentration of the study groups×IMA value. This was done to prevent false negative and false positive causing wide variations in albumin concentrations during pregnancy (62).

Statistical analysis

The data analyzed using Statistical Package for Social Sciences (SPSS) version 25[1]. The continuous data have been assessed for their normality by their skewness (those with skewness ≥1 considered not normally distributed). Normally distributed data presented as mean and standard deviation, while not normally distributed data represented by median and range. Independent t-test (two-tailed) was used to compare the continuous parametric variables between study groups. Mann–Whitney U-test (nonparametric) has been used for comparison of not normally distributed data. Spearman's correlation was used to assess the correlations of adjusted IMA concentration with other criteria in study groups. The correlation was considered weak when the coefficient of correlation (r) (0–0.3), moderate if (r=0.3–0.7), and strong when (r>0.7), if the correlation preceded by (+) sign then the correlation is direct or positive, while if it was preceded by (−) sign then the correlation is inverse or negative.

Receiver operator curve (ROC) used to assess the validity parameters of adjusted IMA concentration for detection of early pregnancy loss. A level of p<0.05 was statistically significant.

RESULTS

The demographic features of the study groups show that in general, the parameters of the normal pregnancy group were higher than its comparatives in the early pregnancy loss group. However, none of these differences reach the significance level, as shown in Table 1.

1 BM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

Table 4: Validity parameters for adjusted ischemia-modified albumin concentration in detecting early pregnancy loss

Variable	Cutoff value	Area under the curve (95% confidence interval)	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
Adjusted ischemia-modified albumin	41.2 ng/ml	0.681 (0.572–0.791)	0.778	0.511	0.614	0.697	0.644

Table 2 illustrates a comparison between the study groups according to the levels of serum albumin and IMA marker, and adjusted IMA. Although albumin concentrations difference between the two groups did not show a significant level, the concentrations of both ordinary IMA and adjusted IMA markers were significantly higher in early pregnancy loss group (p=0.004, p=0.003), respectively.

Table 3 shows no significant correlation between the variables parameters of study groups and adjusted IMA levels.

ROC curve shows the validity parameters for AIMA concentrations in detecting early pregnancy loss, it shows that cutoff value for early pregnancy loss is 41.2 ng/ml with sensitivity 0.77 and specificity 0.51.

In Table 4 shows validity parameters for adjusted IMA concentration in detecting early pregnancy loss in which cutoff value 41.2 ng/ml, area under the curve (AUC) 0.681, sensitivity 0.77, specificity 0.51, positive predictive value (PPV) 0.614, negative predictive value (NPV) 0.697, and accuracy 0.644.

DISCUSSION

Early pregnancy loss is one of the most common complications of pregnancy, with nearly one in four women experiencing an early pregnancy loss in her lifetime [11]. It is responsible for considerable emotional and psychological trauma for patients and their partners [7]. Despite its frequency, its causes are uncertain [3,12].

Multiple studies suggest that there is a considerable evidence that human placentation abnormalities and placental oxidative stress are implicating in the pathogenesis of preeclampsia and increasing evidence indicating that it may also a key factor in early pregnancy loss [5,13,14]. The novel protein, IMA is extensively studied in ischemic heart diseases. The Food and Drug Authority approved its measurement for the extent of cardiac ischemia [15]. IMA levels increased during pregnancy and continued to rise throughout pregnancy suggesting a physiologic oxidative stress which increases gradually, but maternal levels of IMA were higher in pregnancies with defective placental development associated with future preeclampsia, recurrent pregnancy losses (RPLs) during the first trimester, and fetal growth restriction [16]. Some studies suggest using IMA as a marker of placental ischemia. Hence, the biochemical markers that are sensitive and/or specific to ischemia before cell damage consider to be of great clinical importance [17]. Based on these facts, this current case–control study conducts to measure and assesses IMA markers in early pregnancy loss. In the current study, there are no significant differences in general features of the study groups in terms of age, BMI, gravidity, parity, mean gestational age, and number of miscarriages. This agree with Cengiz *et al*. study, there were no statistically significant differences between the groups in terms of age, mean gestational, or BMI, but it Shaw significant differences are found between the groups in gravidity of patients (p=0.001) [18].

In the current study, the mean albumin levels in women with early pregnancy loss are less than albumin levels in normal pregnancy (P-value 0.484) and that agree with Özdemir *et al*. study in which the mean albumin levels in women with early pregnancy loss who had history of RPL were significantly lower than in women in early normal pregnancy (p<0.001) [19]. In the current study, concentrations of both ordinary IMA and adjusted IMA markers were significantly higher in early pregnancy loss group (p=0.004, p=0.003), respectively, and this agreed with multiple studies like Özdemir *et al*. study in it IMA levels were significantly higher in women with early pregnancy loss which had RPL when compared with group of normal pregnancy (p<0.001). Similarly, mean adjusted IMA levels were also higher in RPL as compared with group normal pregnancy (p<0.001) and agreed with Cengiz *et al*. study where the group with early pregnancy loss was found to have significantly higher IMA and adjusted IMA concentrations (p>0.001) for both [18,19].

In current study no significant correlation between the adjusted IMA concentrations and those of other parameters in terms of age, parity, BMI, albumin, and gestational age. This agreed with Cengiz *et al*. study [18].

The current study show validity parameters for adjusted IMA concentration in detecting early pregnancy loss in which cutoff value 41.2 ng/ml, AUC 0.681, sensitivity 0.77, specificity 0.51, PPV 0.614, NPV 0.697, and accuracy 0.644, were in agreement with Cengiz *et al*. study in which a cutoff value of 163 ng/mL, the AUC for the serum adjusted IMA assay reached a value of 0.650 was associated with this value had 75% sensitivity and 55% specificity [18].

CONCLUSION

Adjusted IMA may be used for predicting early pregnancy loss.

ACKNOWLEDGMENT

We would like to thank the Obstetric Department of Al Yarmouk Teaching Hospital/Baghdad and its laboratory for their help. We are also grateful to the patients included in the study.

AUTHORS' CONTRIBUTIONS

All authors were contributed equally in this study.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICAL ISSUES

The study was approved by the Iraqi board for medical specialization.

FUNDING

I have received no funding.

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